Adherence Metrics in the Oral PrEP Clinical Trials: Trends and Takeaways

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Background/Rationale: The full data collection of all oral PrEP studies was conducted in response to a request from the OPTIONS modeling team to collect all published information from studies on oral PrEP in one place, with details about the different adherence metrics and what we know/don't know about what they mean, and efficacy and PK for different modes of transmission. FHI asked that AVAC conduct this data collection. An early version of the spreadsheet was sent to the modeling team to ask for feedback, out of which specific questions on adherence arose and a further focus emerged for the data collation. The following analysis responds to the specific questions posed by the modeling team.

Primary Objective: Review all oral PrEP studies that assess adherence with the aim of addressing the following question: *Which adherence metrics are the most reliable for measuring adherence, and how do we know they are reliable?*

Secondary Objective: Provide a source of data for additional modeling work and other projects to help address questions coming from implementation of oral PrEP (i.e., data on hair sampling can be pulled from this dataset as an adherence metric towards the possibility of using that metric in implementation settings). As questions arise, the data included in this spreadsheet can be used to inform the answers to those questions. OPTIONS can share this dataset with others, including PMM, in order to inform answers to these questions.

Methodology: AVAC collected a total of 189 studies focused on oral PrEP. Peer-reviewed literature (journals and abstracts) was searched for key terms and the snowball method was used. All relevant conference abstract books were mined, in addition to web resources on HIV prevention. Dates of search ranged from 2004 to 2016, with the earliest clinical trial on oral PrEP study starting in 2005.

Data is organized by population and setting (geographic, urban/rural) and by adherence metric used and effectiveness of metric (in-depth-interviews; self-report; PK data; pill count; MEMs cap; pill bottle return) in response to the key questions that arose during the literature review process.

TOPLINE FINDING

Which adherence metrics are the most reliable for measuring adherence, and how do we know they are reliable?

Blood Testing, MEMs caps, and hair sampling were the metrics that best captured accurate adherence figures for patients across the PrEP clinical trials. Both MEMs and hair sampling have demonstrated strong correlations with plasma and DBS TFV/FTC levels in separate studies.

Notably, hair sampling not only provided a reliable measure of adherence, but may also be feasible in many low-resource settings. However, further outreach to the studies that used hair sampling as an adherence metric is warranted in order to assess potential implementation issues with patient resistance or other limitations (i.e., accessibility of hair with common hair styles; cost).

Specific Questions Addressed:

1. What were the specific adherence metrics that were used?
2. Were there other metrics tested in those studies?
3. Did the metrics correlate with PrEP effectiveness?
4. Have they been validated against blood testing?
5. How do they correlate with PrEP effectiveness?

Findings from the Oral PrEP study collection process indicate that the most common adherence measures used were self-report, pill count, PK data and MEMs caps, all of which have been validated against blood testing. Aside from PK data, which we know to be the most accurate, MEMs was best correlated with PrEP effectiveness[1], although pill count was used more frequently. Adherence and product use by self-report was consistently over-reported, but it was not the only measure for which there were serious hindrances in correlation with use. For example, there were a few instances in which difficulty collecting accurate pill count data significantly skewed efficacy data within trials. The most notable and well-documented trial in which pill count failed to accurately measure adherence was FEM-PrEP, where participants hid and/or disposed of unused study pills to give the appearance of adherence[2]. MEMs caps on the other hand offer real-time data on bottle openings; however, many studies note that problems of inaccurate use and user acceptability are key challenges for this method, from the studies collected there were no instances in which MEMs did not correlate with PrEP efficacy.[3] [5]

In terms of testing other metrics, several studies use SMS reminders and reporting for patients to track adherence on intermittent and event-driven dosing regimens. Often combined with timeline follow-back calendar exercises, SMS reporting was useful in the context of event driven dosing regimens, but given its similarities to conventional self-report measures it did not necessarily serve as a good indicator of adherence, and often did not correlate as strongly as MEMs in studies where both metrics were used. [4] [5] [6]

More notably, a number of studies also began implementing hair sample collection as an alternative to blood plasma and PBMCs for PK data. Acceptability of hair sampling among patients was high overall in some studies, while others found patient resistance to providing hair samples, or encountered patients who did not have enough hair to provide.[7] Hair samples not only offer an accurate long-term glimpse at a patient's adherence to PrEP (over weeks and months), but are extremely advantageous in low-resource settings where highly skilled lab technicians, cold storage of samples, and sterile equipment are difficult to procure[7]. However, some studies note that quantifying PrEP levels for both DBS and hair requires equipment for which may be prohibitive in terms of cost. During the iPrEx Open Label Extension, the study team examined the correlation between tenofovir (TFV) emtricitabine (FTC) concentrations in hair and TFV Diphosphate and FTC Triphosphate in dried blood spots, finding strong correlations between hair TFV and TFV-DP levels in DBS ($r = 0.734$; $P < .001$) and hair TFV and DBS FTC-TP ($r = 0.781$; $P < .001$). FTC correlated more strongly with DBS TFV-DP levels ($r = 0.742$; $P < .001$) than with DBS FTC-TP levels ($r = 0.587$; $P < .001$). The correlations between hair measures and the plasma or PBMC measures were high, but generally lower at 8 weeks (range, 0.41–0.51) than 16 weeks (range, 0.61–0.86).[8] Because plasma and PBMC concentrations of TFV/FTC have both demonstrated strong associations with PrEP efficacy across the clinical trials, it is highly possible that hair sampling could serve as a useful pharmacological tool for measuring adherence in the future.[8]

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**See full Oral PrEP Literature Review for all studies used in trends and takeaways analysis*

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